

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No.	:	10/085,539	Confirmation No.:	9853
Applicant	:	CARLYLE, Wenda, et al.		
Filed	:	February 26, 2002		
TC/A.U.	:	1616		
Examiner	:	WEBMAN, Edward J.		
Docket No.	:	P872		
Customer No.	:	28390		
Title	:	PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA LIGAND ELUTING MEDICAL DEVICE		

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF ROBERT L. CAFFERATA
UNDER 37 CFR § 1.131

I, ROBERT L. CAFFERATA, declare the following:

1. I previously was employed by MEDTRONIC, INC., and am one of the inventors of the above-identified application.
2. I understand that in an Office Action dated 14 April 2007, the Examiner rejected Claims 1, 2, 5-7, 9, 11, and 27, of the above-identified application under 35 U.S.C. §103(a) as obvious over the combination of U.S. Patent No. 5,443,458 and International Publication No. WO 01/07066.
3. I understand that International Publication No. WO 01/07066 was filed on 19 July 2000 and published on 1 February 2001. The cover page of International Publication No. WO 01/07066 is attached as EXHIBIT A.

4. Two of my redacted laboratory notebook pages, which were prepared in the United States and witnessed by Wenda Carlyle before 1 February 2001, are attached as EXHIBIT B. The laboratory notebook pages summarize and evidence the reduction to practice of the subject matter claimed in the above-identified application. Specifically, EXHIBIT B, page 1, paragraph 1, describes a stent designed to improve the treatment of restenosis by eluting ligands of peroxisome proliferator-activated receptor gamma (PPAR γ) from the stent. EXHIBIT B, page 1, paragraphs 2 and 6, and page 2, paragraph 1, disclose that rosiglitazone is a PPAR γ ligand and is of particular interest to elute from a stent to treat restenosis.

6. All statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of this application or any patents issuing thereon.



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12-18-07

Date

EXHIBIT A

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
1 February 2001 (01.02.2001)

PCT

(10) International Publication Number
WO 01/07066 A2

- (51) International Patent Classification: A61K 38/00
Research Centre, Ninewells Hospital and Medical School, Dundee, Thyside DD1 9SY (GB).
- (21) International Application Number: PCT/EP00/06986
- (22) International Filing Date: 19 July 2000 (19.07.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
9917405.4 23 July 1999 (23.07.1999) GB
- (71) Applicant (for all designated States except US): THE UNIVERSITY OF DUNDEE [GB/GB]; 11 Perth Road, Dundee, Thyside DD1 4HN (GB).
- (72) Inventors; and
- (73) Inventors/Applicants (for US only): PALMER, Colin, Neil, Alexander [GB/GB]; The University of Dundee, Biomedical Research Centre, Ninewells Hospital and Medical School, Dundee, Thyside DD1 9SY (GB). VOSPER, Helen [GB/GB]; The University of Dundee, Biomedical Research Centre, Ninewells Hospital and Medical School, Dundee, Thyside DD1 9SY (GB). WOLF, Charles, Roland [GB/GB]; The University of Dundee, Biomedical
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GR, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KB, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TI, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— Without international search report and to be republished upon receipt of that report.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS OF TREATMENT AND DRUG SCREENING METHODS

(57) Abstract: A method of preventing or reducing foam cell development from macrophages, or removing foam cells, in a patient, the method comprising administering to the patient an effective amount of an inhibitor of PPAR δ activity. A method of preventing or treating a vascular disease associated with plaque formation and/or thrombotic blockage of the blood vessels in a patient, the method comprising administering to the patient an effective amount of an inhibitor of PPAR δ activity.

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EXHIBIT B

INVENTION: I DISCLOSE A MODIFICATION TO A STENT DESIGNED TO IMPROVE THE TREATMENT OF RESTENOSIS BY ELUTING LIGANDS OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA (PPAR γ) FROM THE STENT. IN ITS SIMPLEST EMBODIMENT, A SINGLE PPAR γ LIGAND IS ADDED TO A STENT BEFORE IMPLANTATION IN A PHARMACEUTICAL NICHES OF RESTENOSIS AFTER STENT DEPLOYMENT IN THE BODY.

RATIONALE FOR CHOOSING PPAR γ LIGANDS: PPAR γ IS A MEMBER OF A NUCLEAR RECEPTOR SUPERFAMILY THAT IS ACTIVATED BY BINDING CERTAIN LIGANDS. THESE LIGANDS CAN BE CHOSEN FROM CERTAIN FATTY ACIDS, LIPIDS AND INSULIN-SENSITIZING THIAZOLIDINEDIONES. SEVERAL PHARMACEUTICAL DRUGS ARE PART OF THIS CLASS: ROSIGLITAZONE, PIOGLITAZONE & TROGLITAZONE.

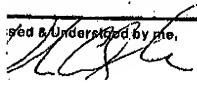
AN IMPORTANT CHARACTERISTIC OF ANTI-RESTENOTIC DRUGS AGENTS IS THEIR ABILITY TO INHIBIT SMOOTH MUSCLE CELL (SMC) PROLIFERATION. PPAR γ LIGANDS ARE KNOWN TO INHIBIT VASCULAR SMC PROLIFERATION PROBABLY BY DIRECT INHIBITION OF CYCLIN-DEPENDENT KINASES (1, 2).

SECOND PROPERTY KEY IN AN ANTI-RESTENOTIC AGENT IS INHIBITION OF SMC MIGRATION (e.g. FROM THE MEDIA TO THE NEOINTIMA OF AN ARTERY). PPAR γ LIGANDS BLOCK MIGRATION OF VASCULAR SMC (3).

THIRD PROPERTY FOR AN ANTI-RESTENOTIC AGENT IS ITS ABILITY TO BLOCK LOCAL VASODILATION/ACTIVATION OF MONOCYTES ~~FOR~~ THEIR SUBSEQUENT SECRETION OF GROWTH FACTORS ~~WHICH~~ ^{THAT} PROMOTE SMC ENTRY INTO THE CELL CYCLE. PPAR γ AGONISTS INHIBIT GROWTH FACTOR PRODUCTION BY MONOCYTES (3). INTERESTINGLY, IT IS KNOWN THAT CERTAIN NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) LIKE SULINDAC ARE ANTI-RESTENOTIC IN ~~IS~~ WITH PLAQUE-LIKE LESIONS (4). THIS COULD BE RELATED TO THE FACT THAT NSAIDs HAVE PPAR γ AGONIST ACTIVITY AT HIGH CONCENTRATIONS (5).

RECENT CLINICAL FINDINGS DEMONSTRATE THAT PATIENTS TREATED SYSTEMICALLY WITH ROSIGLITAZONE HAVE REDUCED NEOINTIMAL PROLIFERATION AT SIX MONTHS AFTER CORONARY STENT IMPLANTATION (6). UNFORTUNATELY THIS DRUG, UNDER THE TRADE NAME RESULIN, IS WITHDRAWN FROM USE IN TREATING TYPE II DIABETES BECAUSE OF EXCESSIVE LIVER INJURY. SINCE PLASMA DRUG LEVELS WERE SIMILAR IN BOTH CASES, IT IS LIKELY THAT THE ANTI-RESTENOTIC EFFECTS OF SYSTEMIC TROGLITAZONE COULD ALSO LEAD TO

Signed & Understood by me,



Invented by

Robert L. Caffarella

Resubmitted by

At 11/1

DEATHS FROM LIVER TOXICITY. ONE OF THE PURPOSES OF THE PRESENT INVENTION REDUCES THE DOSE & BIODISTRIBUTION OF THIS DRUG BY ELUTING IT ^{LOCALLY} FROM A STENT WITHIN THE BODY LUMEN BEING TREATED FOR RESTENOSIS.

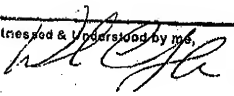
METHODS FOR COMBINING PHARMACEUTICAL DOSAGE FORMS ONTO IMPLANTABLE DEVICES

- PRECIPITATION, CONCENTRATION, CRYSTALLIZATION OF DRUG ONTO THE SURFACE OF STENT (OR WIRE/CHANNELS PLACED IN THE BODY OF THE STENT AS DRUG RESERVOIR CHANNELS) & ACT AS A DIFFUSION-BARRIER TO CONTROL RELEASE OF DRUG
- ADDITION TO THE MATERIAL USED TO COMPOUND SPRING POLYMERIC STENTS.
- CONTACT WITH CHEMICALLY REACTIVE SURFACES (FILMS) BONDED TO THE SURFACE OF THE STENT. ONE SUCH EXAMPLE WAS ANTICIPATED IN RAPID IN-SITU RELEASING "DRUG IMPLANT (PP 7-11).

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6. TAKAGI, T. J. Am Coll Cardiol 2000 36(5):1529-35.

Invented & Improved by me,



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